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(54) Title: PERITONEAL DIALYSIS FLUID

$$[SG]_{m\ (\alpha g)}-[SA] \qquad (1)$$

(57) Abstract: A peritoneal dialysis fluid is provided which comprises a physiologically acceptable aqueous solution containing physiological acceptable inorganic anions and cations and as an osmotic agent, at least one sugar derivative of formula (1) wherein the or each SG, which may be the same or different, represents a residue of a physiologically acceptable metabolizable sugar, SA represents a residue of a physiologically acceptable metabolizable sugar alcohol, m- is greater than 5 and (αg) represents a glycoside linkage that is capable of being cleaved by an α-glycosidase enzyme.

PERITONEAL DIALYSIS FLUID

The present invention relates to novel peritoneal dialysis fluids, capable of inducing an efficient ultrafiltration throughout their dwell time and to the use thereof for performing peritoneal dialysis.

BACKGROUND TO THE INVENTION

In the human body, the transfer of solutes and toxins from one body fluid compartment to another occurs by a variety of chemical and physical processes which include diffusion, osmosis and active transport. In this respect, toxins, excess of water and solutes are transferred from the tissues to the blood stream and then via the arteries to the kidneys. In the kidneys substances to be eliminated may be metabolised and eliminated in the urine

In renal disease, kidney function is not sufficient to maintain an adequate degree of clearance, thus the accumulation of water and uremic toxins occurs in the body. Today, the medical treatments available for patients suffering from a malfunction of the kidney are kidney transplantation, extracorporeal hemodialysis, or alternatively intracorporeal peritoneal dialysis. Treatment by kidney transplantation remains the preferred therapy as the patients may lead a near normal life. Hemodialysis (an extracorporeal procedure) and peritoneal dialysis (an intracorporeal procedure) are the alternative therapies to treat end stage renal disease (ESRD) patients.

Peritoneal dialysis is a well established intracorporeal procedure which is used today as an alternative to the extracorporeal hemodialysis. In fact, in many instances, peritoneal dialysis is preferred to the extracorporeal therapy.

However, in some medical centers, hemodialysis technology is not available and the cost of peritoneal dialysis in general may be lower when other medical complementary care procedures are excluded. For some patients, the surgery required to prepare for permanent blood access has been unsuccessful. Finally, some nephrologist prefer peritoneal dialysis as a hemodialysis procedure,

because it uses a natural membrane and residual (resting) kidney function may be maintained for a longer period after starting the therapy.

In peritoneal dialysis, a dialysis fluid is introduced with the aid of a catheter into the peritoneal cavity in the abdomen of the patient. This catheter is permanently implanted by surgery through the abdominal wall. The peritoneal cavity is flooded with the dialysis fluid, left for an appropriate lapse of time, and then drained.

Peritoneal dialysis relies on the physiological activity of the peritoneum. The peritoneum is a membrane covering the internal abdominal wall and abdominal organs. It is composed of a layer of mesothelial cells, interstitial tissues and blood vessels. This membrane may be used as a semi-permeable exchange membrane in peritoneal dialysis. The peritoneal dialysis procedure involves the introduction of a fluid into the peritoneal cavity for a suitable period of residence time. This allows an exchange of solutes between the dialysate and the blood during the residence time of the dialysate in the peritoneum. This residence time (also called dwell time) varies from patient to patient and can be about five hours. Accordingly, the frequency with which the dialysate has to be exchanged is on average, four to five times per day.

The removal of uremic toxins take place across the peritoneal membrane by diffusion and excess water in the body is removed by osmosis induced by an osmotic agent such as glucose. Glucose is currently the standard osmotic agent and is generally used in a concentration in the dialysis fluid (% weight per volume) of from 1.36 to 4.25.

As indicated, glucose is currently included in the dialysis fluid to impart the necessary osmotic gradient, i.e., it is the standard osmotic agent for dialysis solutions. However, because it is introduced into the peritoneal cavity, it will find its way into the bloodstream during therapy. In fact, glucose crosses the peritoneum so rapidly that the magnitude of the osmotic gradient falls within 2-3

hours after the injection of the dialysate. This causes the unwanted result of water being reabsorbed from the dialysate toward the end of the dialysis period, i.e. before the dialysis fluid is replaced with fresh fluid.

Further, the amount of glucose which is absorbed represent a large portion of the patient's energy uptake, possibly being as high as 15-40%. The clinical consequences are hyperglycemia and obesity. In addition, the sugar has a long term undesirable effects, especially for diabetic patients, for whom there is an additional requirement to increase the injection of the insulin doses or to introduce additional insulin in the dialysis fluid.

A further negative effect of using glucose is the formation of advanced glycation of proteins in diabetic and uremic patients, due to a high concentration of glucose, which is not quickly metabolized. This disadvantage may be the cause of peritoneal membrane damage during therapy and may be also responsible for membrane sclerosis which decreases salt clearance.

This problem was addressed by our International Patent Application No. WO 99/01144 which provides a peritoneal dialysis fluid, containing as an osmotic agent, at least one sugar derivative and physiological acceptable inorganic anions and cations, characterised in that the sugar derivative is a compound of formula

$$[SG]_n\text{-}_{(\alpha g)}\text{-}[SA] \qquad (1)$$

wherein the or each SG, which may be the same or different, represents a residue of a physiologically acceptable metabolizable sugar, SA represents a residue of a physiologically acceptable metabolizable sugar alcohol, n is from 1 to 4 and $\text{-}_{(\alpha g)}\text{-}$ represents a glycoside linkage that is capable of being cleaved by an α-glycosidase enzyme. The adduct of formula (1) is preferably a hydrogenated oligosaccharide. An advantage of the use of such oligosaccharides is that due to their hydrogenated nature, they cannot be glycated, thus, avoiding the complications discussed above.

However, a further problem exists with the present range of osmotic agents prescribed for use in peritoneal dialysis. The majority can only exert an osmotic pressure, capable of inducing ultrafiltration across the peritoneum for a relatively short period of time. For example, when the dialysis fluid containing an osmotic agent is introduced into the peritoneal cavity, it induces a high osmotic pressure. An osmotic gradient therefore exists across the peritoneal membrane, driving a flow of water from the blood into the peritoneal cavity. This facilitates an exchange of solutes between the dialysate and the blood, whilst the dialysate is present in the peritoneal cavity, i.e. throughout the dwell time. Thus, uremic toxins in the blood are carried in this bulk flow of water into the peritoneal cavity where they can be removed. It is therefore clear that the efficiency of such dialysis depends on the maintenance of a suitable osmotic pressure in the peritoneal cavity, throughout the dwell time.

At present this efficiency is undesirably low. For example, the low molecular weight of glucose means that it undergoes rapid trans-peritoneal absorption. Thus, by the end of, say a 4hr dwell period, the majority of the glucose will have passed out of the peritoneal cavity, thus dissipating the necessary osmotic gradient. Consequently, for prolonged dwell times i.e. over-night, the dialysate would therefore need to be exchanged at an inconveniently high frequency. Similarly, the hydrogenated oligosaccharides described in our WO 99/01144 are also either absorbed across the peritoneum or metabolised in the peritoneal cavity to compounds of a low enough molecular weight to pass through the membrane, again providing an inefficient ultrafiltration in, for example, a 6 hr dwell time.

The present application aims to solve with this problem.

Summary of the invention

In a first aspect of the present invention there is provided a dialysis fluid, said fluid comprising a physiologically acceptable aqueous solution containing physiological acceptable inorganic anions and cations and as an osmotic agent, at least one sugar derivative of formula

$$[SG]_{m}\text{—}_{(\alpha g)}\text{—}[SA] \qquad (1)$$

wherein the or each SG, which may be the same or different, represents a residue of a physiologically acceptable metabolizable sugar, SA represents a residue of a physiologically acceptable metabolizable sugar alcohol, m is greater than 5 and —$_{(\alpha g)}$— represents a glycoside linkage that is capable of being cleaved by an α-glycosidase enzyme.

There is no absolute limit on the value of m, but in practice, dialysis fluids according to the invention comprise at least one sugar derivative of formula (1) wherein m is from 5 to 99. Preferably dialysis fluids according to the invention comprise at least one sugar derivative of formula (1) wherein m is from 5 to 20, most preferably from 5 to 10.

Generally, dialysis fluids according to the invention will contain sufficient concentrations of said physiologically acceptable inorganic anions and cations and said at least one sugar derivative for removal of water and solutes from a patient by peritoneal dialysis.

The dialysis fluids of the invention preferably include both sugar derivatives of formula (1) referred to above and the lower molecular weight sugar derivatives described in WO 99/01144. Thus, in a second aspect of this invention a peritoneal dialysis fluid is provided comprising from one, to a plurality of sugar derivatives of formula

$$[SG]_{m}\text{—}_{(ag)}\text{→}[SA] \qquad (1)$$

and from one to a plurality of sugar derivatives of formula

$$[SG]_{n}\text{—}_{(ag)}\text{→}[SA] \qquad (2)$$

wherein SG, SA, —(ag)→ and m are as defined above and n is from 0 to 4.

In a preferred aspect of the present invention a peritoneal dialysis fluid is proposed comprising a plurality of sugars derivatives of formula

$$[SG]_{p}\text{—}_{(ag)}\text{→}[SA] \qquad (3)$$

wherein p is from 0 to 99, preferably from 0 to 20, most preferably from 0 to 10.

Generally dialysis fluids according to the invention comprise from 60-100 g/l of species wherein p is greater than 4, especially of species wherein p is from 4 to 20. More particularly, preferred dialysis fluids according to the invention comprise from 60-100 g/l of species wherein p is from 5 to 20. Most preferably dialysis fluids according to the invention comprise from 60-70 g/l of species wherein p is from 5 to 20.

As regards species with very high molecular weights (i.e. p is greater than 20, these are preferred to be present in very low concentrations (e.g. 0-5 g/l), or more preferably are substantially absent.

Preferred distributions A1 to A6 and B1 to B6 of various molecular weight species are set forth in Tables 1 and 2.

TABLE 1

P	A1	A3	A3	A4	A5	A6
0	0-5	0-5	0-5	1.5-3	1.5-3	1.5-3
1	0-15	0-15	0-15	5-10	5-10	5-10
2	0-20	0-20	0-20	5-15	5-15	5-15
3	0-10	0-10	0-10	2.5-7.5	2.5-7.5	2.5-7.5
4	0-20	0-20	0-20	5-15	5-15	5-15
5	0-30	0-30	0-30	10-20	10-20	10-20
5-20	60-100	60-100	60-100	60-70	60-70	60-70
>20		0-5	0		0-5	0

TABLE 2

P	B1	B2	B3	B4	B5	B6
0	0-5	0-5	0-5	1.5-3	1.5-3	1.5-3
1	5-15	5-15	5-15	8-15	8-15	8-15
2	10-20	10-20	10-20	10-15	10-15	10-15
3	5-10	5-10	5-10	7-9	7-9	7-9
>4	60-100			60-100		
4-20		60-100	60-100		60-100	60-100
>20			0			0

Preferably, the compounds of the above formulae (1) - (3) are hydrogenated oligosaccharides (particularly hydrogenated α-D-oligosaccharides). Especially preferred are such compounds wherein the or each SG represents a glucose residue.

The term "hydrogenated oligosaccharide" is used herein to refer to compounds defined by of any of the formulae (1) - (3), such usage does not necessarily mean that the substances in question have been prepared or manufactured by hydrogenation of an oligosaccharide starting material, although such a method of preparation is possible. Thus the compounds represented by these formulae may be prepared by chemical or enzymatic procedures in which the residues of formulae [SG] and [SA] are linked together, or different [SG] and [SA] residues are exchanged for one another.

For example, where hydrogenation procedures are used, a compound for example, of formula

$$[SG]_p \xrightarrow{(\alpha g)} [SG]$$

may be hydrogenated to form a compound of formula

$$[SG]_p \xrightarrow{(\alpha g)} [SA] \quad (1)$$

Similarly, the term "sugar alcohol" as used herein, is used interchangeably with the term "polyol" to refer to residues obtainable by hydrogenating sugar residues.

Although we do not wish to be restricted to any particular theory, it is believed that the sugar derivatives of formula (1) provide osmotic agents which not only have too large a molecular weight to pass through the peritoneal membrane, but are also slowly metabolised, whereby allowing them to exert a sustained osmotic pressure throughout a prolonged dwell time. The sugar derivatives in effect function as a slow release osmotic agents, in that, they are initially catabolized to compounds which also exert an osmotic pressure and which are also too large to travel through the peritoneum. Thus, by the time the sugar derivatives are ultimately degraded to glucose etc., (which can escape across the peritoneum), dialysis will be almost complete.

The invention in its more specific aspects relates to the application of hydrogenated α-D-oligosaccharides, including at least one compound having 5 to 10 sugar (preferably glucose) residues, as new osmotic agents in peritoneal dialysis. These compounds are advantageous over the presently available osmotic agents because they can maintain the necessary osmotic gradient across the peritoneum for a superior length of time. Thus, facilitating for example, over night dialysis. This is compared to osmotic agents such as glucose, which can induce a suitable osmotic gradient however, it is soon disipated due to the absorption of glucose through the peritoneal membrane.

Preferred aspects of the invention are based upon specific choices of the glucosyl arrangement of the oligosaccharide alcohol, upon the number of glucosyl groups, on the identities of the terminal polyols (sugar alcohols), and on the proportion in the mixture of different polyols.

In accordance with preferred aspects of this invention, hydrogenated oligosaccharides having α-D-glucosyl arrangement, with (1-->6) or (1-->4) glucosyl linkages, in which the non-reducing sugar at the end of the glucosyl arrangement has been hydrogenated, are used to make dialysis solutions.

These hydrogenated alpha-D-oligosaccharides used according to the invention include, but are not limited to those which can be isolated as a naturally existing entity, or can synthetically be derived by known chemical or enzymic reactions from available natural carbohydrate substrates. They desirably result from the modification of natural carbohydrates.

Thus, in carrying out the invention, the manufacture of the preferred hydrogenated alpha-D-oligosaccharides may be based on
(i) transglycosidation to form (1-->6) and (1-->4) glycoside linkages and replacement of constituent monosaccharides by a different building blocks, or
(ii) chemical reduction of carbonyl groups into a corresponding polyol moiety.

These resulting preferred hydrogenated alpha-D-oligosaccharides can be used in a dialysis fluid in a homogeneous form or as mixtures, but the fluid must contain at least one hydrogenated oligosaccharide with more than 4 sugar residues. Between five and twenty glucose units plus one terminal polyol (i.e. a unit at the end of the glucosyl chain) is preferable. Thus, in the formulation of dialysis solutions based on hydrogenated oligosaccharides, suitable mixtures may comprise $[GP]_{(5\text{-}20)}$-sorbitol and optionally $[GP]_{(0\text{-}4)}$-sorbitol and/or $[GP]_{(21\text{-}99)}$-sorbitol.

In such mixtures the sorbitol moieties may be replaced wholly or in part by xylitol, ribitol or glycerol.

The sugar alcohols or polyols are preferably ones which are readily metabolized in humans. Examples include glucytol (sorbitol), xylitol, ribitol, and glycerol.

Such, oligosaccharide alcohols with the defined specified terminal sugar alcohols or polyols, may be mixed in proportions to ensure that the respective end metabolites remain below the metabolic capacity of the (usually uremic) patients being treated. The oligosaccharide alcohols used in the invention include those which can be isolated as naturally existing entities, or ones which can synthetically be derived using known chemical or enzymic reactions from available natural carbohydrate substrates.

The preferred composition for the proposed osmotic agent is a plurality of sugar derivatives of formula

$$[SG]_{\underline{p}\ (aq)}\text{—}[SA] \qquad (3)$$

wherein $\underline{p}$ is from 0 to 99, whereby the majority of the dialysate will be made up from hydrogenated alpha-D-oligosaccharides possessing from 5 to 20 glucosyl units plus a non-reducing terminal sugar alcohol or polyol unit.

The average molecular weight (determined as the geometrical mean of the distribution of MW in the mixture) of such a preferred composition is in the region of 600 - 20,000 Daltons, obtained principally by the relatively large proportion of GP_4-sorbitol(MW 830), GP_5-sorbitol (MW 992) and $>GP_6$-sorbitol (MW > 1164).These high molecular weight compounds have the advantages that the transperitoneal absorption is less than for example sorbitol and $GP_{(1-4)}$-sorbitol, and after hydrolysis in the circulation there are less polyols generated. Therefore, the osmolality and metabolic half life is relatively reduced compared to the lower molecular weight forms.

Preferably, up to 60 grams of hydrogenated oligosaccharide form may be present per liter of peritoneal dialysis solution. This range of concentrations can be used for all formulations irrespective of the molecular weight of the hydrogenated oligosaccharide and irrespective of what mixtures are used.

In the preferred molecular weight range of 600-20,000, various concentrations may be used to achieve the desirable osmolality and ultrafiltration. Thus, the amount of sugar derivative in this molecular weight range used per liter of peritoneal dialysis fluid may be 60 grams, preferably 10 to 50 g and most preferably 35 to 45g. Added to a standard peritoneal dialysis solution containing physiological salt concentrations, this represents an osmolality range between 280 milliOsmol/kg and 405 milliOsmol/Kg.

Table 3 below, shows examples of dialysis fluids for use in the present invention with preferable proportions(by weight, totalling 100)/concentrations of hydrogenated oligosaccharides, defined according to formula (3):

$$[SG]_{p\ (aq)} \rightarrow [SA]$$

wherein Dialysis Fluids 2 and 3 are most preferred.

Table 1

p	Dialysis Fluid 1		Dialysis Fluid 2		Dialysis Fluid 3	
	Proportion %	Conc. g/l	Proportion %	Conc. g/l	Proportion %	Conc. g/l
0	0 - 5	0 - 5	0 - 5	0 - 5	1.5 - 3	1.5 - 3
1	5 - 15	5 - 15	5 - 15	5 - 15	8 - 15	8 - 15
2	10 - 20	10 - 20	10 - 20	10 - 20	10 -15	10 -15
3	5 - 10	5 - 10	5 - 10	5 - 10	7 - 9	7 - 9
4 - 6	60 - 80	60 - 80	60 - 80	60 - 80	60 - 70	60 - 70
7 - 10			0	0	0	0

Most preferably the dialysis solutions are aqueous solutions with a pH between 5.4 and 7.4, and preferably in the physiological range of from pH 7.0 to 7.4.

The solutions of this invention may contain typical physiological inorganic salts which are commonly used in peritoneal dialysate solution, e.g. sources of Na^+, K^+, Ca^+, Mg^{2+} and Cl^- ions. Buffers to be used in the solution to achieve the correction of the metabolic acidosis can include lactate, bicarbonate, pyruvate or a combination of these.

As the proportion of the hydrogenated oligosaccharides is normally in the range of about 1 to 6% by weight of the dialysate solution, it can be added to a water solution containing typically from 116 to 140 mEq/liter of sodium, 0 to 5 mEq/liter of calcium, 95 to 144 mEq/liter of chloride, and 5 to 40 mEq/liter of bicarbonate and/or pyruvate and/or lactate.

The use of hydrogenated oligosaccharides reduces the body load of glucose by approximately 40-60%, resulting in a lower energy uptake. For example, during peritoneal dialysis with both hydrogenated disaccharides and/or

trisaccharides formulations, the circulating free fatty acids (a parameter reflecting the caloric intake) decreased to 50% as compared to use of a glucose peritoneal solution. This may reduce the elevated triglycerides in patients receiving glucose peritoneal dialysis.

The use of the hydrogenated oligosaccharides as osmotic agents has advantages in respect to their biocompatability and cytotoxicity. Since the hydrogenated oligosaccharides can be provided at a more physiological pH, and the hydrogenated oligosaccharides are not metabolized in the peritoneum (forming glucose), no alteration of cell function (such as cell inhibition) tends to take place during therapy.

However, the novel advantage of the osmotic agents provided in this invention is that they diffuse at a reduced rate through the peritoneal membrane. This is principally due to their high molecular weight and also partly due to the lack of receptors for hydrogenated oligosaccharides in mesothelial and endothelial cells of the peritoneum, which would otherwise accelerate their transport. Further, an osmolarity of 250 - 550 MilliOsmol/kg may be achieved by adding osmotic agents according to the invention, e.g. $[GP]_{(5-99)}$-Sorbitol to a standard peritoneal dialysis solutions

On introduction of the dialysis medium according to the invention into the peritoneal cavity by a catheter, an osmotic gradient is induced across the peritoneum. This is due to the fact that the peritoneal cavity now has a much greater osmolality than the surrounding plasma, carried in the blood vessels lining the peritoneum. Solutes are carried along with this bulk flow of water (a process known as ultrafiltration, solvent drag), additionally driven by hydrostatic pressure and their relative concentration gradients. This osmotic gradient therefore facilitates the removal of toxins and a restoration of the appropriate electrolyte balance in plasma, achieved by exchange of the solutes with the dialysate in the peritoneal cavity. Thus, it is clear that the efficiency of the dialysis is dependent in part, on the osmotic gradient induced across the peritoneum.

As indicated, the dialysis fluids of the invention are superior to fluids that are currently available. In this regard it will be appreciated that the majority of osmotic agents used today get absorbed through the peritoneum, either by

1. Diffusion, due to their low molecular weight and concentration gradients, for example GP_1-sorbitol, glucose

2. By metabolism in the peritoneal cavity to metabolites able to diffuse through the membrane , i.e. GP_2-sorbitol

3. By transport mechanisms available to them in the peritoneum i.e. glucose.

The result being that the osmotic gradient induced by such agents is maximal during the start of a dialysis exchange and decreases during the dwell because the osmotic agent is absorbed from the dialysate. For example, glucose absorption averages 61 % of the instilled quantity during a 4-hour dwell and 75 % after 6 hours. The absolute but not the relative absorption is influenced by the glucose concentration used. As a consequence, the transcapillary ultrafiltration rate has its maximum value at the start of dialysis and decreases during the dwell time.

However the hydrogenated oligosaccharides of the present invention have a higher degree of polymerisation i.e. preferably containing 5 or 6 glucosyl residues. Thus, they are not readily absorbed through the peritoneum. Additionally they are principally metabolised by enzymes which are not present in the peritoneum and therefore their breakdown to low molecular weight compounds is minimal during the average dwell time of 4hrs. Dialysis fluids containing these agents can therefore maintain an efficient ultrafiltration throughout a prolonged dwell time, possibly even over night. This is compared to currently available dialysis fluids where the dialysate must be periodically and frequently exchanged during the dwell time.

This is illustrated in the in-vivo results of Comparative Study 1. For example, in a 4 hour dwell time the absorption of hydrogenated oligosaccharides in Dialysate 1, containing a mixture of 60g/l of $GP_{(0-99)}$-sorbitol, was between 42.6 - 51.1%. Surprisingly however, this value was only 9 - 26% for Dialysate 2, containing a mixture of 60g/l of $GP_{(0-6)}$-sorbitol. Similar results were found in an in-vivo study utilising an 8hr dwell time, adsorption was 73.6% for Dialysate 1 but only 27.5% for Dialysate 2.

Lower molecular weight hydrogenated oligosaccharides are generally more capable of inducing a high osmotic pressure than those comprising a higher number of glucosyl units. Thus, the preferred composition of hydrogenated oligosaccharides for use in a dialysate, provided in this invention, is a mixture of compounds defined by $GP_{(0-99)}$-sorbitol, wherein $GP_{(5)}$-sorbitol and $GP_{(>5)}$-sorbitol are in the higher proportion.

The hydrogenated oligosaccharides of the invention may, as indicated, be supplied and used as a dialysis fluid. However, a peritoneal dialysis solution containing hydrogenated oligosaccharides may be prepared in a solid form by freeze drying. Before use in peritoneal dialysis the dry material is reconstituted by dissolution in sterile and pyrogen free water.

Thus in accordance with a further aspect of the invention there are provided compositions for use in preparing a peritoneal dialysis fluid as defined herein, by reconstitution by addition of sterile, pyrogen free water, said composition comprising the specified components in dry form or in the form of an aqueous concentrate.

The invention further provides a method of performing peritoneal dialysis which comprises perfusing the peritoneal membrane with a peritoneal dialysis fluid as defined herein.

Additionally, the invention provides the use of a compound or a plurality of compounds defined by formulae (1) to (3)

$$[SG]_{m}\text{—}_{(\alpha g)}\text{—}[SA] \qquad (1)$$

$$[SG]_{n}\text{—}_{(\alpha g)}\text{—}[SA] \qquad (2)$$

$$[SG]_{p}\text{—}_{(\alpha g)}\text{—}[SA] \qquad (3)$$

in the manufacture of a peritoneal dialysis fluid.

Comparative Study 1

The purpose of this in vivo study was to evaluate the ultrafiltration and peritoneal absorption of the proposed dialysis solution, Dialysis Fluid 1 (comprising hydrogenated oligosaccharides defined by $GP_{(0\text{-}99)}$-sorbitol) compared to that of a dialysis solution defined by $GP_{(0\text{-}4)}$-sorbitol, Dialysis Fluid 2, in a rabbit model.

Female New Zealand rabbits weighing 2700-4000g and aged from 80-120 days were used in all the experiments. Briefly, anaesthesia was introduced and maintained by inhalation of an isoflurane/oxygen mixture via an endotracheal tube. The rabbit's body temperature was maintained at 37-41°C throughout the experiment. A 12-gauge Braunuele cannula was inserted just paramedian to the linea alba, the sharp part being replaced with a plastic part once the muscle layer had been passed, which was then induced further. Peritoneal dialysis fluid was then administered via the peritoneal cannula. For example, for a 4000g body weight, 200-400ml of peritoneal medium was administered. After 0, 4, and 8 hours, blood and peritoneal fluid samples were taken for high performance chromatography analysis and the animal was weighed. Thus allowing evaluation of changes in protein, saccharide and electrolyte content as well as volume, during dialysis. Samples were taken after abdominal massage for even distribution of fluid within the peritoneal cavity, free-flow from the cannula was enabled for 3-5ml or aspirated: the volume was documented and then a sample of 0.5-1ml was collected for laboratory analysis. Any removed fluid was

replaced, thus, keeping the hematocrit stable. Collection of blood samples and their replacements were performed via a vessel in the ear, for replacement a vein cannula is placed and connected to an infusion system.

Two dialysis fluids, 1 and 2, were tested and their compositions were as defined in Table X.

Table X

Component	Dialysis Fluid 1	Dialysis Fluid 2
$>GP_5$-sorbitol	16.82 g/l	0
GP_5-sorbitol	11.31 g/l	0
GP_4-sorbitol	9.88 g/l	18.86 g/l
GP_3-sorbitol	4.90 g/l	8.80 g/l
GP_2-sorbitol	7.89 g/l	15.28 g/l
GP_1-sorbitol	8.00 g/l	15.68 g/l
Sorbitol	1.19 g/l	1.38 g/l
Sodium	134 mM	134 mM
Calcium	1.25 mM	1.25 mM
Magnesium	0.5mM	0.5 mM
Chloride	98.5 mM	98.5 mM
Hydrogencarbonate	36 mM	36 mM
Lactate	3 mM	3 mM

The results are shown in Tables Y and Z.

Table Y shows the change in concentration and the percentage absorption of the sugar derivatives in Dialysis Fluid 1 after a dwell period of 4 or 8 hours in the peritoneal cavity. This table shows that during a 4hr dwell time between 9 and 26% of the hydrogenated oligosaccharides were absorbed. While during an 8hr dwell, 27.5% was absorbed.

Table Z shows the same information as Table Y but concerns tests utilising Dialysis Fluid 2. The results show that during a 4hr dwell time between 42.6 and 51.1% of the hydrogenated oligosaccharides were absorbed. While during an 8hr dwell, 73.6% was absorbed.

TABLE Y

Animal	Time of Sample	PD-Volume ml	Dialysis Fluid 1 Composition							Total sugar derivatives + sorbitol	Total absorption of sugar derivatives + sorbitol after dwell time
			Sorbitol mg/ml	DP1-sorbitol mg/ml	DP2-sorbitol mg/ml	DP3-sorbitol mg/ml	DP4-sorbitol mg/ml	DP5-sorbitol mg/ml	>DP5-sorbitol mg/ml		
	Before injection		1.19	8.00	7.89	4.90	9.88	11.31	16.82		
1	Immediatel y after injection, t=0 t=4hrs	 270 289	 1.8 1.10	 6.3 5.52	 8.4 5.53	 5.93 7.68	 9.38 7.69	 11.92 8.64	 16.18 14.83	 16.2 14.7	 9.3%
2	t=0 t=4	260 300	1.8 3.7	7.2 3.12	8.12 4.91	4.6 5.11	9.40 5.45	10.22 8.34	17.70 15.12	15.4 13.7	 11%
3	t=0 t=4	240 325	1.54 0.29	7.87 1.17	8.23 1.83	4.59 1.54	8.05 4.91	9.73 6.04	16.69 13.49	13.6 10.2	 25%
4	t=0 t=4	280 485	1.45 0.48	15.17 1.62	5.21 2.02	3.48 1.35	7.16 2.17	9.64 4.97	17.86 9.79	16.8 12.4	 26%
5	t=0 t=4 t=8	380 536	1.15 0.31 0.11	11.4 18.07 6.69	6.93 6.08 3.56	3.06 1.32 0.81	8.95 9.23 5.68	10.6 3.31 1.99	17.09 15.83 11.56	22.5 16.3	 27.5%

TABLE Z

Animal	Time of Sample	PD-Volume ml	Dialysis Fluid 2 Composition							Total sugar derivatives + sorbitol	Total absorption of sugar derivatives + sorbitol after dwell time
			Sorbitol mg/ml	DP1-sorbitol mg/ml	DP2-sorbitol mg/ml	DP3-sorbitol mg/ml	DP4-sorbitol mg/ml	DP5-sorbitol mg/ml	>DP5-sorbitol mg/ml		
	Before injection		1.38	15.68	15.28	8.8	18.86	0	0		
6	Immediately after injection, t=0	270	1.6	15.35	15.20	8.40	18.22	0	0	15.87	45.5%
	t=4hrs	310	0.68	2.25	6.38	6.50	12.11	0	0	8.65	
7	t=0										
	t=4	270	1.8	15.22	14.50	8.6	18.50	0	0	15.4	42.6%
		330	0.44	2.17	5.75	7.11	11.30	0	0	8.83	
8	t=0										
	t=4	260	1.4	15.12	14.8	8.4	18.11	0	0	15.0	50.0%
		340	0.33	2.17	3.83	6.3	9.4	0	0	7.49	
9	t=0										
	t=4	270	1.68	15.17	14.88	8.4	18.21	0	0	15.75	51.1%
		335	0.56	3.22	4.6	5.3	9.20	0	0	7.7	
10	t=0	280	1.22	15.3	15.11	8.21	18.22	0	0	16.25	
	t=4		0.41	2.66	3.55	4.11	9.35	0	0		73.6%
	t=8	310	0.44	3.33	2.52	2.31	5.22	0	0	4.28	

Conclusion: Both Dialysis Fluids 1 and 2 showed some extent of absorption during dwell indicating that there must have consequently been a reduction in ultrafiltration. However, this absorption was over 50% higher for Dialysis Fluid 2, indicating that Dialysis Fluid 1 was superior and maintained an efficient ultrafiltration rate during the entire dwell time of 4 to 8 hours.

Claims

1. A peritoneal dialysis fluid, said fluid comprising a physiologically acceptable aqueous solution containing physiological acceptable inorganic anions and cations and as an osmotic agent, at least one sugar derivative of formula

$$[SG]_{m}\text{—}_{(\alpha g)}\text{—}[SA] \qquad (1)$$

wherein the or each SG, which may be the same or different, represents a residue of a physiologically acceptable metabolizable sugar, SA represents a residue of a physiologically acceptable metabolizable sugar alcohol, m is greater than 5 and $\text{—}_{(\alpha g)}$ represents a glycoside linkage that is capable of being cleaved by an α-glycosidase enzyme.

2. A peritoneal dialysis fluid according to Claim 1 comprising at least one sugar derivative of formula

$$[SG]_{m}\text{—}_{(\alpha g)}\text{—}[SA] \qquad (1)$$

and at least one sugar derivative of formula

$$[SG]_{n}\text{—}_{(\alpha g)}\text{—}[SA] \qquad (2)$$

wherein SG, SA, $\text{—}_{(\alpha g)}$ and m are as defined in Claim 1 and n is from 0 to 4.

3. A peritoneal dialysis fluid according to Claim 1 or Claim 2 comprising a plurality of sugars derivatives of formula (1).

4. A peritoneal dialysis fluid according to any preceding claim comprising plurality of sugar derivatives of formula (2).

5. A peritoneal dialysis fluid according to any preceding claim wherein m is from 5 to 99.

6. A peritoneal dialysis fluid according to Claim 5 wherein m is from 5 to 20.

7. A peritoneal dialysis fluid according to Claim 6 wherein m is from 5 to 10.

8. A peritoneal dialysis fluid according to any preceding claim comprising a plurality of sugar derivatives of formula

$$[SG]_{p}^{\leftarrow (ag)} [SA] \qquad (3)$$

wherein p is from 0 to 20.

9. A peritoneal dialysis fluid according to Claim 8 wherein the different sugar derivatives are present in proportions by weight (totalling 100) in the following ranges

p	Proportion, %
0	0 - 5
1	5 - 15
2	10 - 20
3	5 - 10
>4	60 - 100

10. A peritoneal dialysis fluid according to Claim 8 wherein the different sugar derivatives are present in proportions by weight (totalling 100) in the following ranges

p	Proportion, %
0	0 - 5
1	5 - 15
2	10 - 20
3	5 - 10
4-20	60 - 100
>20	0

11. A peritoneal dialysis fluid according to Claim 10 wherein the different sugar derivatives are present in proportions by weight (totalling 100) in the following ranges

p	Proportion, %
0	1.5 - 3
1	8 - 15
2	10 - 15
3	7 - 9
4-20	60 - 100

12. A peritoneal dialysis fluid according to any preceding claim wherein the concentrations of the different sugar derivatives are in the following ranges

p	Concentration, g/l
0	0 - 5
1	0 - 15
2	0 - 20
3	0 - 10
4	0 - 20
5	0-30
>5	60-100

13. A peritoneal dialysis fluid according to any preceding claim wherein the concentrations of the different sugar derivatives are present in the following ranges

p	Concentration, g/l
0	0 - 5
1	0 - 15
2	0 - 20
3	0 - 10
4	0 - 20
5	0 - 30
5-20	60 - 100
>20	0 - 5

14. A peritoneal dialysis fluid according to Claim 13 wherein the concentrations of the different sugar derivatives are present in the following ranges

p	Concentration, g/l
0	1.5 - 3
1	5 - 10
2	5 - 15
3	2.5 - 7.5
4	5 - 15
5	10 - 20
5-20	60-70

15. A peritoneal dialysis fluid according to any preceding claim wherein the compounds of formulae (1) to (3) are hydrogenated oligosaccharides.

16. A peritoneal dialysis fluid according to any preceding claim wherein the or each SG represents a glucose residue.

17. A peritoneal dialysis fluid according to any preceding claim wherein SA represents a residue of a sugar alcohol selected from sorbitol, xylitol, ribitol and glycerol

18. A peritoneal dialysis fluid according to any preceding claim having a pH in the range from 5.4 to 7.4, preferably from 7.0 to 7.4.

19. A peritoneal dialysis fluid according to any preceding claim containing the following concentrations of the specified inorganic ions:

Na^+	116-140 mEq/l
Ca^+	0-5 mEq/l
Cl^-	95-144 mEq/l

20. A peritoneal dialysis fluid according to any preceding claim containing a total of 5 to 40mEq/l of buffering counterions selected from bicarbonate, pyruvate and lactate ions, or a mixture of these.

21. A peritoneal dialysis fluid according to any preceding claim containing from 1 to 60 g/l of said sugar derivatives.

22. A peritoneal dialysis fluid according to Claim 21 containing from 10 to 50 g/l, preferably 35 to 45g/l of said sugar derivatives.

23. A peritoneal dialysis fluid according to any preceding claim having an osmolality of 250 to 550 milliOsmols/l, preferably 300 to 500 milliOsmols/l.

24. A peritoneal dialysis fluid according to any preceding claim comprising sugar residues linked by (1-->6) or (1-->4) glycoside linkages.

25. A peritoneal dialysis fluid according to any preceding claim comprising a sugar residue linked to a sugar alcohol residue by a (1-->6) or (1-->4) glycoside linkage.

26. A peritoneal dialysis fluid according to any preceding claim comprising an aqueous solution containing a mixture of rogenated oligosaccharides, said hydrogenated oligosaccharides having terminal sugar alcohol residues selected from sorbitol, xylitol, ribitol and glycerol.

27. A peritoneal dialysis fluid according to any preceding claim containing from 125 to 140 mEq/l of sodium, from 90 to 125 mEq/l of chloride, from 1 to 5 mEq/l of calcium, from 0.2 to 5 mEq/l of magnesium, and from 25 to 40 mEq/l of a buffering anion selected from lactate, pyruvate and bicarbonate or a mixture of these.

28. A peritoneal dialysis fluid according to any preceding claim, having an osmolality of 280 to 455 milliosmols per litre.

29. A composition for use in preparing a peritoneal dialysis fluid as claimed in any preceding claim by reconstitution by addition of sterile, pyrogen-free water, said composition comprising the specified components in dry form or in the form of an aqueous concentrate.

30. A method of performing peritoneal dialysis which comprises perfusing the peritoneal membrane of a patient with a peritoneal dialysis fluid as defined herein.

31. The use of a sugar derivative, or a plurality of sugar derivatives of formulae (1) to (3) as defined in any preceding claim, in the manufacture of a peritoneal dialysis fluid.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/081005 A3

(54) Title: PERITONEAL DIALYSIS FLUID

$$[SG]_{m\ (\alpha g)}-[SA] \qquad (1)$$

(57) Abstract: A peritoneal dialysis fluid is provided which comprises a physiologically acceptable aqueous solution containing physiological acceptable inorganic anions and cations and as an osmotic agent, at least one sugar derivative of formula (1) wherein the or each SG, which may be the same or different, represents a residue of a physiologically acceptable metabolizable sugar, SA represents a residue of a physiologically acceptable metabolizable sugar alcohol, m- is greater than 5 and $\overline{(\alpha g)}$ represents a glycoside linkage that is capable of being cleaved by an α-glycosidase enzyme.

INTERNATIONAL SEARCH REPORT

P../GB 02/01560

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P43/00 A61K33/14 A61M1/28 //(A61K33/14,33:10,33:00, 31:70,31:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 01144 A (ALLIED THERAPEUTICS) 14 January 1999 (1999-01-14) cited in the application claims 1,2,5,6,8-15,22,24,25,27	1,2,4,8, 15-29
A	DATABASE WPI Week 199918, 1999 Derwent Publications Ltd., London, GB; AN 1999-210747 XP002231286 BAXTER: "Dialysis solution of peritoneum-contains alicyclic hexavalent alcohol, hexonic acid or saccharic acid and/or saccharide derivatives" & JP 11 049671 A (BAXTER INT INC), 23 February 1999 (1999-02-23) abstract	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2003	10/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01560

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 30 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01560

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9901144 A	14-01-1999	AU 8229798 A	25-01-1999
		BR 9815225 A	21-08-2001
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JP 11049671 A	23-02-1999	NONE	